Toxicology of PCBs for Mammals and for Birds

by J. G. Vos*

Introduction

In the early days of its use, little work was done on the toxicology of the PCBs, and this was only in relation to the risks of occupational exposure. As will be shown many more studies were made as soon as it appeared that the extremely stable PCB's became a threat to the environment and its wildlife, and accidents occurred of acute poisoning in man and animals. These studies have been made with material with different contents of chlorine, from different manufacture, and—as we can now say in retrospect—with different and unknown contents of toxic impurities. For this reason the toxicological information of PCB's is difficult to summarize, but since the character of some important impurities has recently been elucidated, it is well to discuss these first in order to be able to consider their contribution to the overall toxicity of the different preparations studied.

These studies were started because of the analogy between the effects of the PCBs (1–6) and some toxic effects associated with toxic factors in crude chlorophenols and in "toxic fat". Effects of the latter are liver damage (7), chloracne (7,8) and edema formation (9).

Chemical, Toxicological, and Pathological Identification and Evaluation of Toxic Impurities in Technical PCB Preparations

The first indication of the presence of toxic impurities was obtained in a comparison of the toxicity of three commercial PCB samples (containing 60% chlorine on the average): Phenoclor DP6 (sample I), Clophen A60 (sample II) and Aroclor 1260 (sample III). These three mixtures showed a marked resemblance in their gas chromatograms and mass spectra (10). In this comparative feeding test in one-day-old chicks (11), it was found that 100% mortality, subcutaneous and abdominal edema, and centrolobular liver necrosis occured in only two groups (fed the samples I and II). Hydropericardium (Fig. 1), a common effect of these two mixtures, was only occasionally seen in the chicks fed the sample III. The

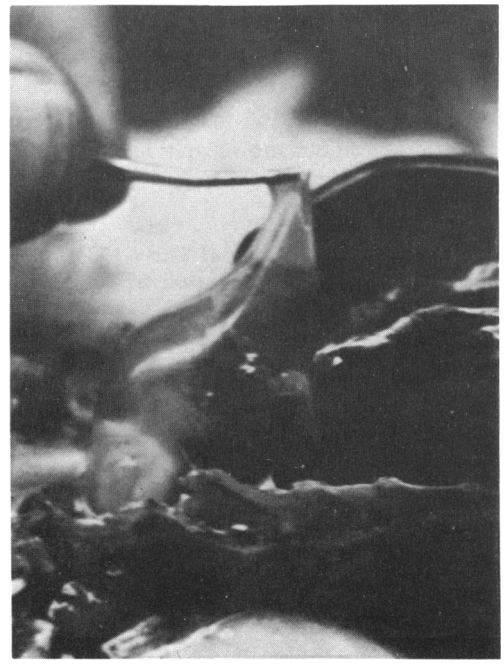

FIGURE 1. Hydropericardium in a chick fed 400 ppm of sample I.

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Table 1. Mortality, and Pathologic Observations of Chicks Fed 400 ppm PCB for 60 Days.

PCB sample	N	Number of deaths	Number of birds with edema			Number of birds with liver necrosis
			Hydro-pericardium	Abdominal	Subcutaneous	
I	24	24	18	8	5	9
II	22	22	20	9	7	9
III	20	3	3	0	0	0
Control	20	0	0	0	0	0

mortality in this group was only 15% (Table 1). The excretion of coproporphyrin and protoporphyrin in the feces was increased. Examination of tissues under Wood's light showed the presence of red fluorescence indicating porphyrins in the liver and other tissues of especially the birds that died. This hepatic porphyria was found in all three experimental groups.

In the subsequent study (12) by means of column and gas-chromatography the presence of relatively more polar compounds was demonstrated in the 25% diethylether fraction of samples I and II. In a chick embryo assay (Table 2), the difference in toxicity between the three samples was confirmed; the high toxicity of the 25% diethylether fraction of sample II is demonstrated by the similarity between the mortality levels in the group injected with 3.5 sample II/egg and the group injected with the 25% diethylether fraction from 3.5 mg sample II/egg.

Mass spectrometric analysis revealed that identical chlorinated compounds were present in the 25% diethylether fraction from samples I and II but not in that from sample III. They included compounds with mass number 304 and 338. The proposed identity of these compounds, tetrachlorodibenzofuran and pentachlorodibenzofuran, is indicated by the following chemical-analytical, pathological, and toxicological data.

Table 2. Chick-Embryo Assay of Three PCB samples and the 25% Diethylether Fraction from Sample II

PCB sample	Dose (mg/egg)	Number of eggs treated	Percentage hatch of fertile eggs
I	3.5	15	0
II	3.5	20	5
III	3.5	15	80
Fraction from sample II	35	15	0
	3.5	15	7
	0.35	15	92
	0.035	15	100
Ethanol control	0	20	94
Untreated control	—	20	90

From exact mass measuremen's it was found that the formulae of these peaks were $C_{12}H_4O^{35}Cl_4$ and $C_{12}H_3O^{35}Cl_5$. The formulae of the fragment ions 241 and 275 were $C_{11}H_4{}^{35}Cl_3$ and $C_{11}H_3{}^{35}Cl_4$. From this data it can be concluded that the parent ion has a preferential fragmentation for the loss of a single ClCO unit. Mass spectra were compared with the spectrum of a chick edema factor 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin. The mass spectrum of this compound has a similar fragmentation pattern, i.e. the loss of two successive mass units of 63 suggests a loss of two ClCO units. With microcoulometric analysis a certain maximum level could be indicated. This maximum level was found to be five ppm of the compound with mass number 338 in sample II and 20 ppm in sample I.

Polychlorinated dibenzofurans are strong hepatotoxic and acnegenic compounds. Tri- and tetrachlorodibenzofurans in a single oral dose of 0.5 — 1.0 mg/kg caused severe and often lethal liver necrosis in rabbits (7,13), and application to the ear resulted in chloracne. Tetrachlorodibenzodioxin was about 10 times more toxic (7). Injection of the 25% diethylether fraction obtained from 35 mg sample II into the aircell resulted in 100% mortality (Table 2). It can be calculated that the maximum dose/egg is 0.2 μg pentachlorodibenzofuran (taking five ppm as the maxi-

mum value). This confirms the order of toxicity found by Higginbotham et al. (9) in the case of chloro-dibenzodioxins. Tetra and pentachloridibenzofurans were considered responsible for the higher toxicity of samples I and II.

Confirmation is also obtained from the subsequent comparative toxicity study in rabbits (14). Again samples I and II were more toxic; the liver and skin lesions were more severe. Porphyria, especially of the liver, was present in all three groups (Fig. 2). A remarkable finding was the intense red fluorescence of small foci inside hepatic cells. They probably represent nuclei. This was confirmed in an additional cell culture experiment with the Aroclor sample and with 2,4,5,-2′,4′,5′-hexachlorobiphenyl. (This experiment was carried out by my colleague Dr. J. G. Wit of the Biochemical Section).

Application of the 25% diethylether fraction on the skin of rabbits resulted also in differences in toxicity (Fig. 3). So the presence of the hepatotoxic and acnegenic polychlorinated dibenzofurans as impurities in samples I and II was found to be established.

In another experiment (15), the toxicity of the Aroclor (60% Cl) sample was compared with the toxicity of 2,4,5,2′,4′,5′-hexachlorobiphenyl. From the increased fecal excretion of coproporphyrin in both experimental groups (Table 3), it is very likely that PCBs themselves are responsible for the porphyrogenic action of crude preparations. From the presence of slight skin lesions induced by 2,4,5,2′,4′,5′-hexachlorobiphenyl when compared with the Aroclor sample, it can be concluded that the major acnegenic action of crude mixtures comes from a possible contamination with chlorinated dibenzofurans. It can also be concluded that PCBs themselves have a slight acnegenic action. Liver damage was essentially the same after treatment with both 2,4,5,2′,4′,5′-hexachlorobiphenyl and the Aroclor mixture. The conclusion that the liver injury, caused by crude preparations, is predominantly due to the contaminants, is based on the differences in liver toxicity between the three PCB preparations (11,14).

The probable contribution of polychlorinated dibenzofuran (PCF) and pure polychlorinated biphenyl (PCBs) in the toxicity of crude preparations is summarized in Table 4. A proper evaluation of toxicity data and residue data can be hindered by the possibility that PCB samples may

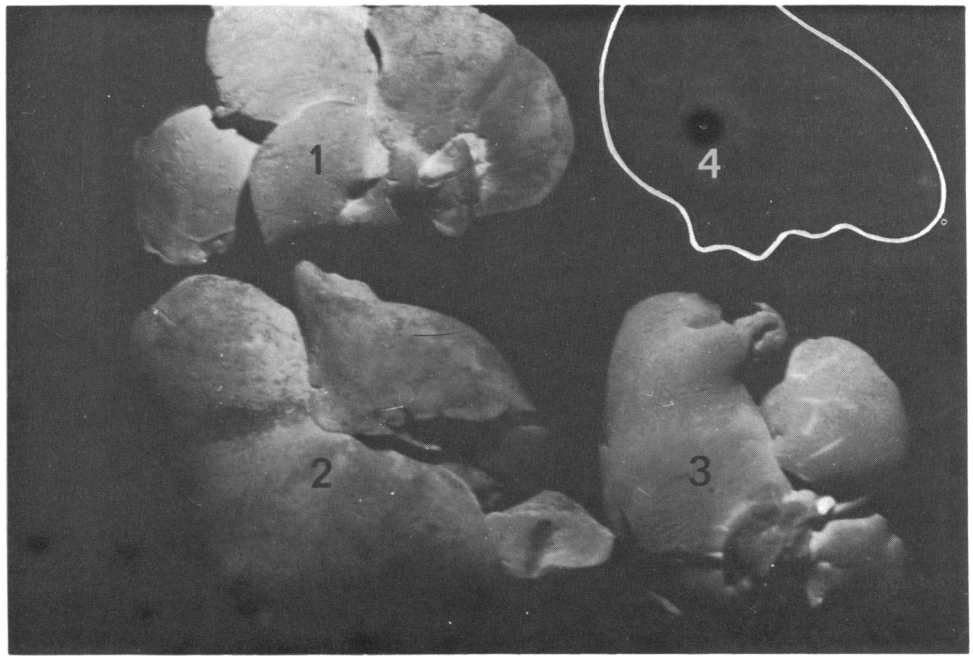


FIGURE 2. Fluorescence of porphyrins under ultraviolet light in livers from rabbits treated with 60% chlorinated PCB's, 1, Aroclor; 2, Clophen; 3, Phenoclor; and 4, Control liver (14).

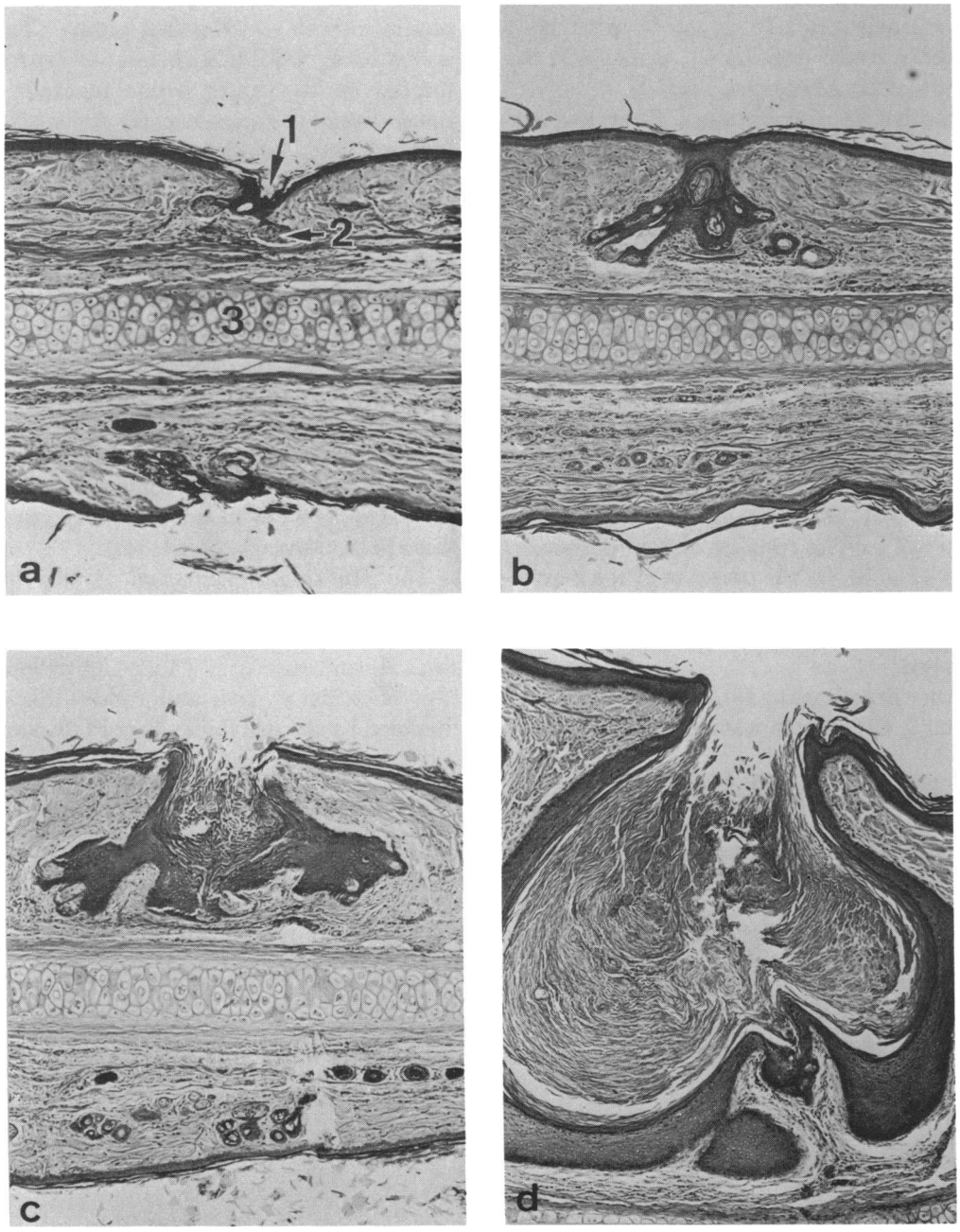


FIGURE 3. Response of the inside of the rabbit's ear after topical application of the 25% diethylether fractions from technical PCB's. Haemotoxylin and eosin. ×60. (a) Skin of control animal treated with ethanol. Note the hair follicle at 1, seabaceous gland tissue at 2, and cartilage at 3. (b). Ear skin of the animal treated with the fraction from sample III. Some hyperplasia and hyperkeratosis of the follicular epithelium can be seen. (c). Ear skin of the rabbit treated with the fraction from sample II. Considerable hyperplasia and hyperkeratosis of the follicular epithelium. (d). Ear skin of the rabbit treated with the fraction from sample I. Part of a section that shows the most severe lesion. The gravity of the response was in general the same as seen in (c). Note the cystic dilated hair follicle with prominent hyperplasia and hyperkeratosis of the follicular and epidermal epithelium (14).

differ in an important respect: the presence of toxic impurities. The possibility of distinguishing between the effects of PCBs and their impurities can be further improved by using pure isomers with known positions of the chlorine atoms.

Mortality, Liver Effects, Edema Formation and Other Effects

These data, as presented by different authors, are summarized in Tables 5, 6, and 7. As can be seen in Table 5, the acute and subacute toxicity data of PCB's are poor. The established values are high. Semichronic oral toxicity studies are summarized in Table 6. Dermal and inhalation studies are given in Table 7.

Table 3. Coproporphyrin Contents (μg/g Dry Weight) of Feces of Rabbits Treated with PCB for 4 weeks, and of Controls.[a]

2,4,5,2',4',5'-Hexachlorobiphenyl	Aroclor (60% Cl)	Control
45.0	24.1	4.5
6.2	5.0	3.7
20.8	29.4	3.6
39.6	16.0	3.5
Mean 27.9[b]	18.6[b]	3.8

[a] Figures are the contents of feces, collected from the cecum of the individual animals.

[b] Significantly different from controls, $P \leq 0.025$.

It is very probable that the results of these studies may have been influenced by the presence of polychlorodibenzofurans or other toxic impurities. For example, in the study of Rehfeld et al. (23) general edema was already found in chicks fed 30 ppm Aroclor 48% Cl, while Kohanawa and co-workers (22) noted edema formation at the 100 ppm level of another 48% chlorinated mixture. Mortality in the latter study was also lower (Table 6).

Liver Effects

The most important liver effects, summarized in Tables 5, 6, and 7, are weight increase, fatty degeneration, hyalin degeneration and necrosis. Increased liver weights, as noted in several studies,

Table 4. Probable Contribution of Polychlorinated Dibenzofuran (PCF) and Pure Polychlorinated Biphenyl (PCB) in the Toxicity of Crude PCB Mixtures.

	Chloracne	Edema formation	Liver damage	Hepatic porphyria
Polychlorinated Dibenzofuran	++	++	++	−
Polychlorinated Biphenyl	+	−	+	++

Table 5. Acute and Subacute Oral Toxicity Studies of PCB Preparations.

Preparation	Animal	Treatment	Mortality	Liver effects	References
Unknown	Mouse	single dose of approx. 2000 mg/kg	LD50		(16)
Aroclor 54% Cl	Rat	single dose of 500 mg/kg	0%	Increase of weight and lipid; potentiation of CCl_4 toxicity	(17)
Aroclor 42, 54, 60, and 68% Cl	Mallard	single dose of 2000 mg/kg	0%		(18)
42% Cl	Rat	20 daily doses of 138 mg	0% in 3 months	Hyalin bodies in liver cells	(19)
42% Cl	Guinea pig	2 doses of 69 mg 1 week apart	100% between 11 and 29 days	Fatty metamorphosis; central atrophy	(19)
65% Cl	Rat	6 daily doses of 300 mg	70% in 14 days	Increase of weight; cell swelling: hyalin granules	(20)

Table 6. Semichronic Oral Toxicity Studies of PCB Preparations.

Preparation	Animal	Treatment	Mortality	Liver effects	Other effects	References
65% Cl	Rat	Doses of 50 mg every second day	60% in 5 weeks	33% weight increase; cell swelling; hyalin globules		(20)
48% Cl	Cynomolgus monkey	From 641 mg in 40 days to 348 mg in 239 days	not given	Enlargement; SER proliferation	Main cause of death: pneumonia or diarrhea	(21)
48% Cl	Squirrel monkey	From 320 mg in 46 days to 67 mg in 48 days	not given	Enlargement; SER proliferation SER proliferation	Main cause of death: pneumonia or diarrhea; palpebral edema in 1 animal	(21)
48% Cl	Mouse	Daily doses of 0.001 ml for 13 to 26 weeks	0%	Enlargement; SER proliferation RER reduction; myelin figures; increase of microbodies, lysosomes and lipid	Skin: loss of hair, erosion and ulceration after 3 months	(21)
Aroclor 42% Cl	Chicken	100, 200, 400, and and 1000 ppm in diet for 4 weeks	0, 0, 50, 90, and 90% respectively	Enlargement; damage at the higher levels	Edema formation from 200 ppm; at high levels internal haemorrhage and tubular dilatation in kidneys	(5)
Aroclor 42% Cl	Chicken	200 and 400 ppm in diet for 3 weeks	0 and 12% respectively		Pronounced edema at 400 ppm; enlarged kidneys; small spleen; defeathering and dermatitis	(6)
48% Cl	Chicken	1, 5, 10, 25, 50, 100, 300, 600, 1200, 2400, and 4800 ppm in diet for 20 days	0% from 1 to 100 ppm; 100% from the 100 ppm level		Edema formation 100 ppm level	(22)
Aroclor 48% Cl	Chicken	10, 20, 30, 50, 100, and 150 ppm in diet for 4.5–5 weeks	After 3 weeks: 0, 0, 30, 30 and 20%; at the end 0, 0, 80, 60, and 80% respectively	Enlargement	General edema and depression of the secondary sexual characteristics from the 30 ppm level	(23)
Aroclor 54% Cl	Chicken	250 and 150 ppm in diet for 6 to 13 weeks	250 ppm 100% between 3 and 10 weeks; 500 ppm some mortality at the end		500 ppm at end: comb weights 20-fold and testes weights 2-fold lower than controls	(24)
Aroclor 54% Cl	Bengalese finch	Estimated dose rate at 56 days of 254 mg/kg/day	50%		Hydropericardium in some birds	(25)
Phenoclor 60% Cl	Japanese quail	2000 ppm in diet	100% between 6 and 55 days		Hydropericardium	(10)

Table 7. Dermal Toxicity and Inhalation Studies of PCB Preparations.

Preparation	Animal	Treatment	Mortality	Liver effects	Skin effects	References
42% Cl	Guinea pig	11 daily skin applications of 34.5 mg	100% between 11 and 21 days	Fat; central atrophy; perinuclear basophilic granulation; focal necrosis in a few animals	Occasional thickening of the epidermis	(19)
42% Cl	Rabbit	Skin application at alternate days, total dose from 946 to 1980 mg	100% between 17 and 98 days	Fatty degeneration; central atrophy	Thinning of prickle cell layer and thickening of outer cornified layers	(19)
Aroclor	Rabbit	Daily skin applications of 0.3, 0.6, and 0.9 g	High dose died before liver necrosis developed	Moderate doses: mottled liver, subacute yellow atrophy, fatty degeneration, and marked necrosis	Reddening; formation of small papules and blisters; finally desquamation of external epidermal layers	(26)
Aroclor 65% Cl	Rat	Inhalation of 0.57 mg/cubic meter for 16 hours for 37 to 134 days	0%	Pale and yellow; cell swelling; hyalin degeneration; potentiation of CCl_4 and C_2H_4OH toxicity		(20)

are well explained by the proliferation of smooth surfaced membranes of the endoplasmic reticulum (SER) as was found by Nishizumi (21) in mice and monkeys and by Norback and Allen (27) in rats. The latter workers found a proliferation of the SER in rats fed PCB for 1 to 5 weeks. Concomitant with the structural changes, the activities of measured drug metabolizing enzymes (nitroreductase and aromatic hydroxylase) were increased. The induced level of drug metabolizing activity persisted as the proliferation of the SER decreased and concentric arrays pervaded the cytoplasmic reticulum (27). These concentric membrane arrays, probably representing the hyalin bodies described by Bennet et al. (20) and Miller (19), could have an enzymatic function similar to that associated with the SER (27).

Similar formations, the so-called myelin figures, were demonstrated in mouse liver by electron microscopy; in monkey liver they were not found (21). In both mouse and monkey liver a proliferation of the SER was found. In our comparative dermal toxicity study (15) in rabbits with 2,4,5,2′,4′,5′-hexachlorobiphenyl and Aroclor (60% Cl), the light microscopic findings included necrosis, hydropic degeneration (Figs. 4 and 5) as well as a peripheral and perinuclear shift of cell organelles (Fig. 5) and focal cytoplasmic hyalinization. In electron microscopy, the shift was found to be due to a proliferation of the SER resulting in a displacement of rough surfaced membranes (RER) and mitochondria. The focal cytoplasmic hyalin degeneration, often seen in hydropic cells, was recognized as tightly packed tubules of proliferated SER (Fig. 6). This very probably represents hypertrophic, hypoactive SER.

Sublethal effects caused by induction of hepatic enzymes have been noted by several authors. Increased steroid metabolism in pigeon liver homogenates has been demonstrated by Risebrough et al. (28). Lincer and Peakall (29) confirmed the effect of PCB on the hormone metabolism in birds at very low dose levels. They fed kestrels for 5 months with Aroclor 54% and 62% Cl at levels of 0.5 and 5.0 ppm. The higher

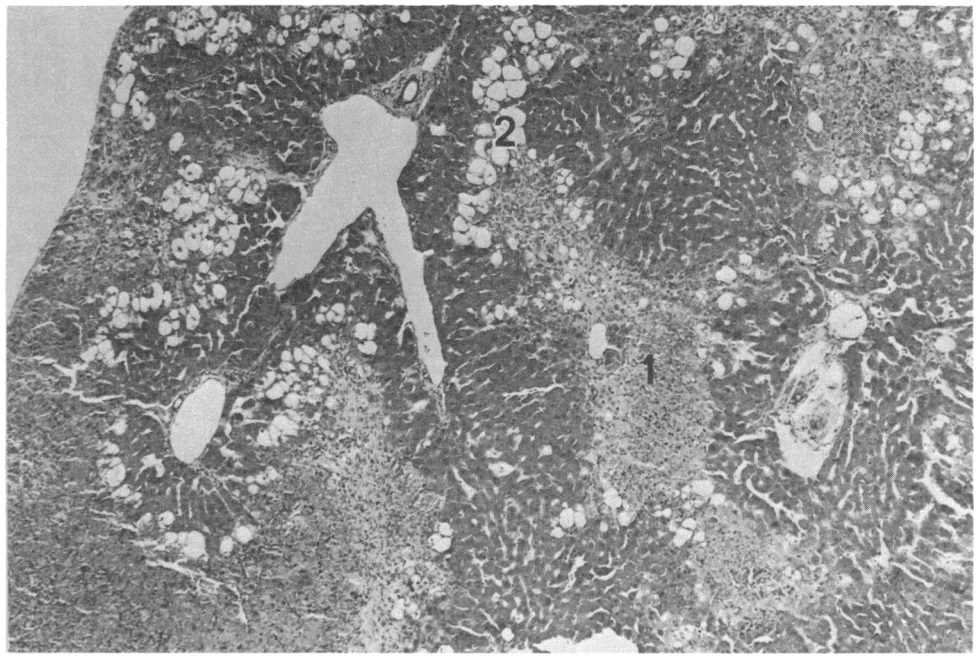


FIGURE 4. Liver damage in a killed rabbit treated with 120 mg Aroclor (60% Cl), 5 times per week, for 28 days. Note the centrolobular necrosis (1) and the hydropic cells (2) at the margin of the necrotic and vital tissue. Haemotoxylin and eosin. ×150.

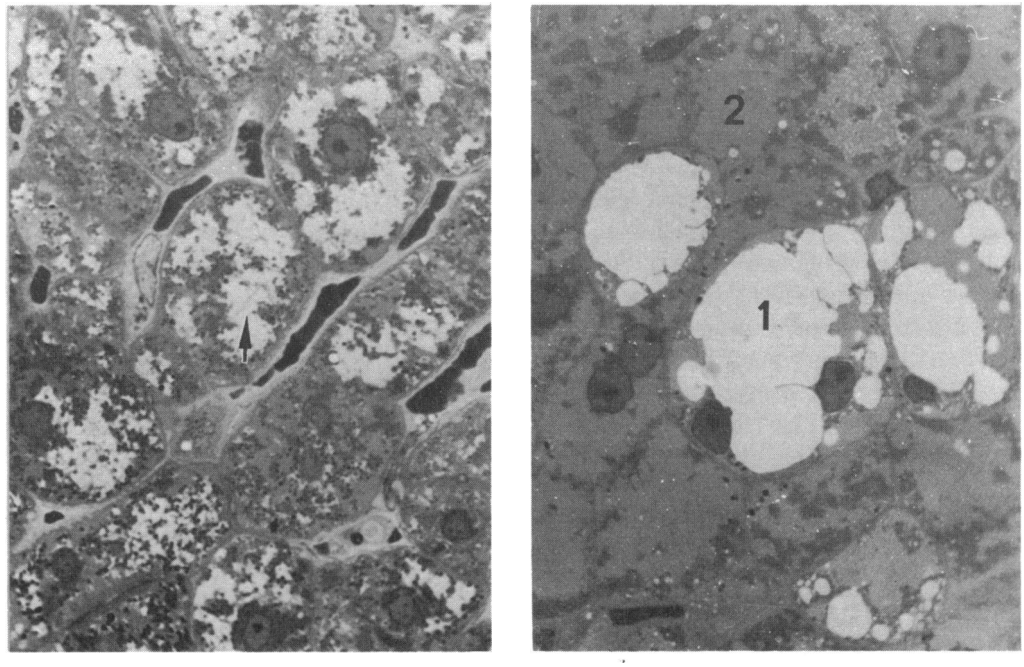


FIGURE 5(a). Liver cells of a control rabbit. Clear areas may represent negative images of glycogen (arrow). Toluidine blue. ×940. (b). Liver cells of an Aroclor treated killed rabbit. Note the hydropic cells (1) and the perinuclear and peripheral displacement of cell organelles with sometimes hyalin foci (2) inside hepatic cells. Toluidine blue. ×940.

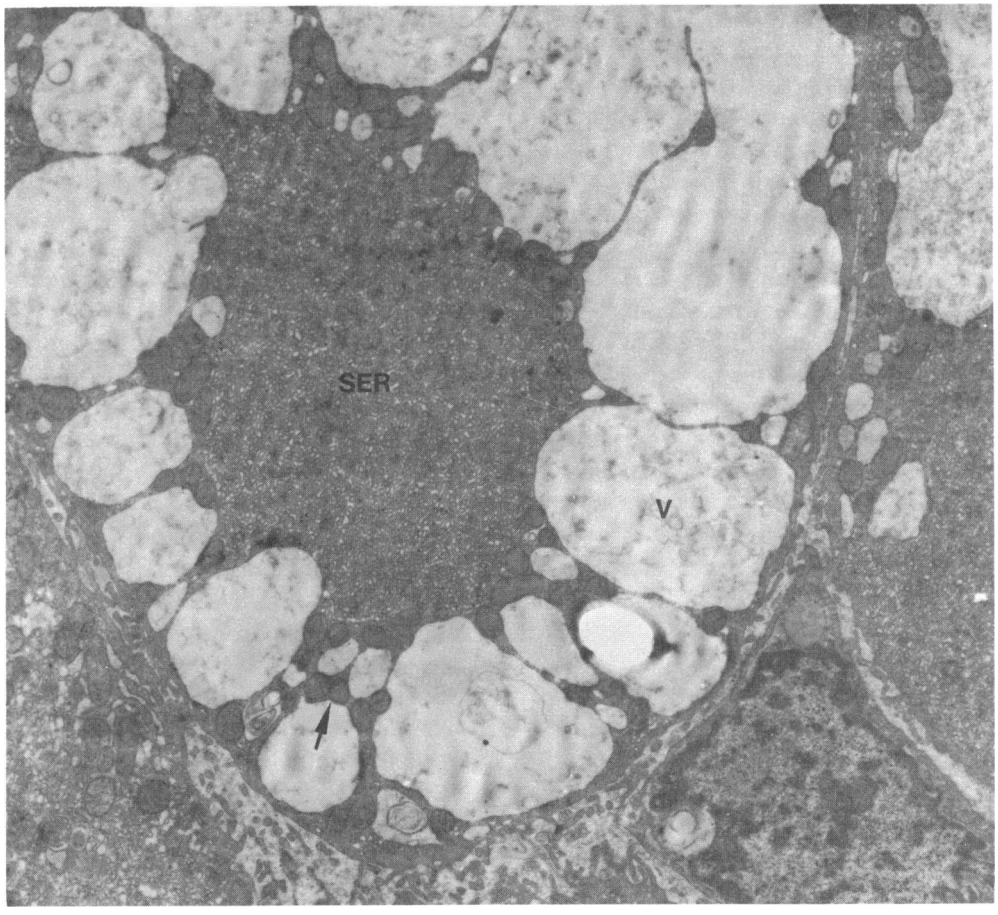


FIGURE 6. Hydropic liver cells from the same animal as seen in Figure 5b showing a large number of vacuoles (V) and a perivacuolar localization of mitochondria (arrow). Note the strong proliferation of the SER, consisting of tightly packed tubules. Uranyl acetate and lead citrate. ×5500.

dose being roughly equivalent to 2 mg/kg PCBs to each kestrel. A dose dependent in vitro breakdown of estradiol to a more polar metabolite occurred in the livers from kestrels fed either Aroclor 1254 or Aroclor 1262. No such conversion took place in the livers of the control birds. The increase in hepatic enzyme activity correlated with an increase in cytoplasmic RNA, as was measured cytophotometrically. A shortened sleeping time after treatment with hexobarbital, and enhanced in vitro rates of aniline hydroxylation and p-nitroanisole demethylations were demonstrated by Street and coworkers (30). These authors also found an increase of these effects with increasing chlorine content of the different PCB preparations (Aroclor 21 to 68% Cl).

Using enzyme induction as parameter, no-effect levels of some PCB preparations were established in the rabbit, rat, and Japanese quail. Oral administration of Aroclor 21% Cl and 54% Cl (1.0 and 10 mg/kg) for 28 days to pregnant rabbits resulted in liver enlargement and increased activities of the drug metabolizing enzymes aniline hydroxylase and aminopyrine n-demethylase at the 10 mg/kg level of the 54% chlorinated Aroclor. The no-effect level for enzyme induction in the pregnant rabbit appeared to lie between 1.0 and 10 mg/kg in the case of Aroclor 54% Cl, and higher than 10 mg/kg for Aroclor 21% Cl (31).

Another parameter for enzyme induction was used by Komatsu and Tanaka (32). They found that the hexobarbital induced sleeping times in rats were reduced by pretreatment with PCBs.

The minimal effective dose was 5 mg/kg for 3 days with Kanechlor 400 (48% Cl) and 2 mg/kg for 3 days with the higher chlorinated Kanechlor 500. The porphyrogenic action of PCBs was further evaluated in a study with Japanese quail (33). The results (Table 8) indicate that the hepatic porphyria is closely associated with an increase of mitochondrial ALA synthase activity. A significantly increased activity of this enzyme was already noted after administration of daily doses of 1 mg/kg Aroclor 60% Cl for 1 week. Mean PCB content of the liver at that dose was 1.41 ppm. A less sensitive parameter is tissue fluorescence due to excess quantities of porphyrins. Liver fluorescence was only seen at the 100 mg/kg level. It develops, probably, only in animals showing clinical symptoms, such as loss of weight. A similar finding was done in the prior experiment with chickens (11).

Edema Formation

The most striking finding in birds is the accumulation of fluid. The pathogenesis of the edema formation is discussed by Flick and coworkers (6). The primary site of the edema causing factor could be the heart by increasing the permeability of the vascular bed, leading to cardiac congestion. Pulmonary edema could be the result of the cardiac congestion. The pulmonary edema might be followed by a flow of fluid into abdominal and subcutaneous air sacs. Decreased serum protein values (34) could also contribute to the edema formation. Liver damage can be responsible for reduced serum albumin levels.

As mentioned in Table 4, the edema formation is probably due to the presence of polychlorodibenzofurans. In our study the edema formation by the 60% chlorinated Aroclor sample was minimal at the 400 ppm level. As can be seen in Table 6, chick edema-like lesions were noted at low feeding levels and were caused by lower chlorinated Aroclors. Therefore the presence of toxic impurities in these Aroclor samples has to be considered.

Other Effects

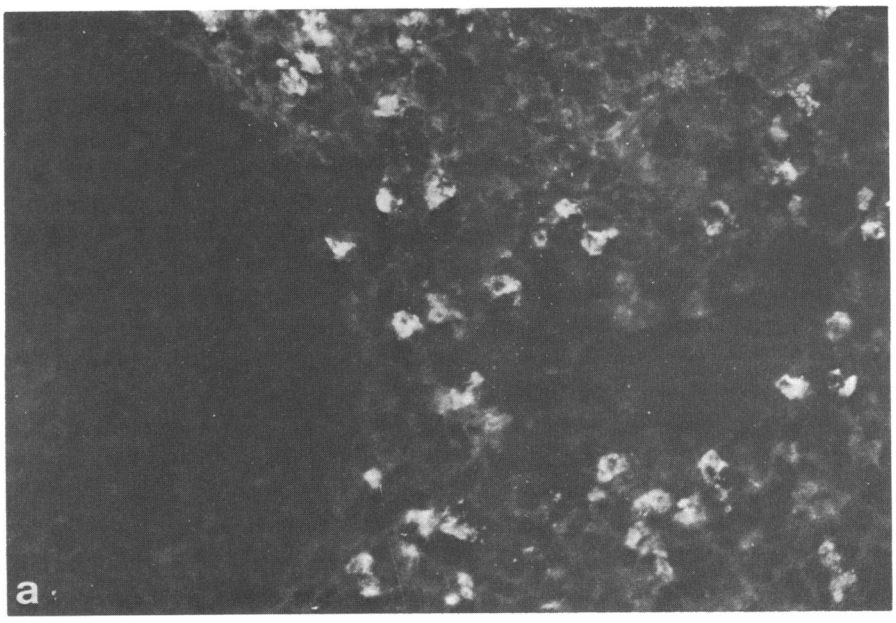
An interaction of PCBs with duck hepatitis virus was found by Friend and Trainer (35). Ten-day-old ducklings were fed a 54% chlorinated Aroclor mixture at levels of 25, 50 and 100 ppm. The birds suffered no apparent clinical intoxications. Five days later they were challenged with duck hepatitis virus, and they suffered significantly higher mortality than birds which were not exposed to PCBs.

Effects of PCBs on the lymphoid system were noted in some studies. Feeding of PCBs to chickens resulted in small spleens (6,11). Lymphopenia, atrophy of the cortex of the thymus, and a reduction in the number of germinal centers in spleen and lymph nodes was found in rabbits (14). Therefore, an immunosuppressive action could be present. In an experiment with guinea pigs, this was established (36). Feeding of 10 ppm Aroclor 60% Cl, for 8 weeks resulted in a

Table 8. Formation of δ-Aminoevulinic Acid by Liver Mitochondria, Liver Residues, and Tissue Fluorescence in Female Japanese Quail Orally Dosed with PCB for Seven Days.

Aroclor (60% Cl) (mg/kg body weight)	ALA formed (mμ moles ALA/g liver/hr)	PCB content liver (ppm)	Tissue fluorescence incidence	
			Macroscopic	Microscopic (liver)
0	6.46±1.64	0.15[c]	0/5	0/5
0.1	8.76±4.06	0.45±0.27	0/5	0/5
1	10.50±1.21[b]	1.41±0.67	0/5	0/5
10	17.3±6.4[b]	27.0±9.4	0/5	0/5
100	119.9[c]	478±294	3/5	2/5

[a] Mean values±SD, 5 birds per group.
[b] Significantly different from controls, P≦0.01.
[c] Pooled samples



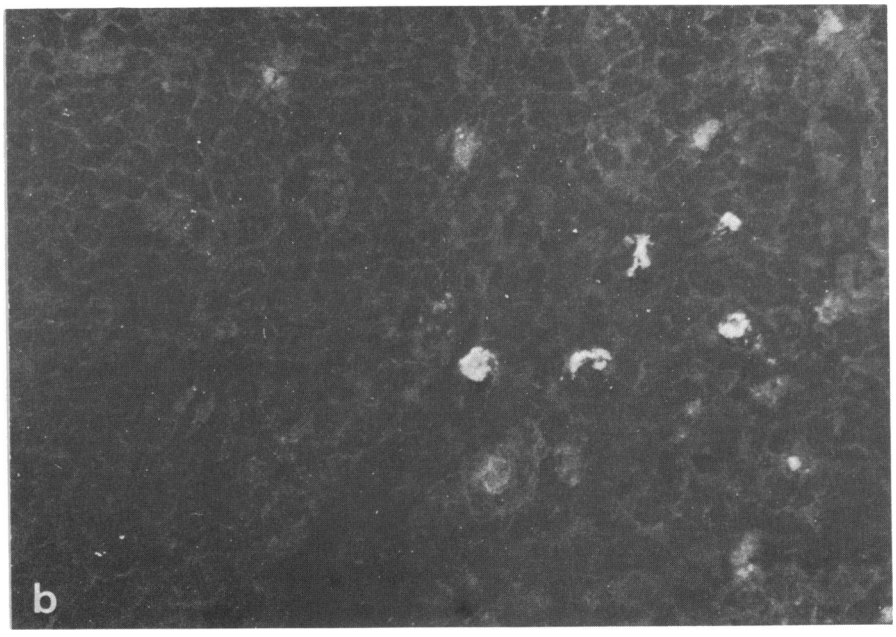


FIGURE 7. Representative areas of tetanus toxoid stimulated popliteal lymph nodes of guinea pigs. (a) Large number of antibody forming cells in a control animal. (b). Reduced number of antibody forming cells in an animal fed 10 ppm Aroclor (60% Cl) for 8 weeks. Direct fluorescent antibody technique. Cryostat sections. × 375. (36).

decreased number of antibody-forming cells in the popliteal lymph node, after stimulation of the humoral lymphoid system with tetanus toxoid (Fig. 7). This suppression may explain the higher sensitivity of PCB-fed ducklings for duck hepatitis virus (35). In a comparative toxicity study in guinea pigs, an indication for an effect of PCB (Clophen and Aroclor 60% Cl) on the cell-mediated immunity was obtained. Feeding of these mixtures at 50 ppm levels for 6 weeks resulted in a decreased number of circulating lymphocytes (unpublished data).

An estrogenic activity of PCBs (Aroclor 21–48% Cl) was demonstrated by Bitman and Cecil (37). The estrogenic activity was evaluated using the 18-hr glycogen response of the immature rat uterus after a single subcutaneous injection. The minimum effective dose was 8 mg. The higher chlorinated PCB mixtures were inactive at the 8 mg level. In the above mentioned subacute feeding study of 60% chlorinated mixtures in guinea pigs, we found significantly increased uterus weights in the PCB treated animals. Both increased steroid metabolism, as mentioned by Rehfeld and coworkers (23), and the estrogenic activity could be responsible for the depression of secondary sexual characteristics (decreased development of comb and wattles) noted in cockerels (24).

Administration of Aroclor (54% Cl) at levels of 12.5, 25, and 50 mg/kg body weight during the first 28 days of gestation had embryotoxic effects in the rabbit (31). Edema and beak deformities in chicken embryos have been described after yolk-sac injection of 10 and 25 mg 42% chlorinated Aroclor, resulting in respectively 95 and 100% embryonic mortality (38).

An effect of PCB on the nervous system was noted by Ogawa (39). Oral administration of PCB (0.3–0.5 ml/kg/day) to rats for 14 or 21 days, resulted in marked or moderately impaired motor function, decreased motor conduction velocity and loss of large nerve fibres. He concluded that PCB caused neuropathy in rats.

Conclusion

Because of the possible presence of polychlorinated dibenzofurans (PCF) or other toxic impurities in crude PCB preparations, it is difficult to interpret many of the toxicity studies. Pure samples are required for comparative investigations. Also the fate of the toxic impurities in the environment has to be determined. As presented here, PCBs have several sublethal effects, such as microsomal enzyme induction, porphyrogenic action, estrogenic activity, and immunosuppression. Since porphyria seems to be an effect of PCBs themselves and not from PCF, the induction of ALA synthase could be used as criterion in the approximation of a no-effect level (at least for the 60% chlorine type of PCBs). The no-effect level could be about 0.1 mg/kg (mean PCB content of the liver in Japanese quail about 0.2 ppm). This is in the same order of magnitude as found in the other studies. Additional research is needed to determine fully the significance of these sublethal effects. Moreover, chronic and reproduction studies are necessary. The present results also make clear that manufacture of commercial PCB mixtures that are free from impurities is urgently requested.

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